REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. CLAIM STATUS AND AMENDMENTS

Claims 1-37 were pending in this application when last examined. Claims 1-15 and 18 were examined on the merits and stand rejected. Claims 16, 17 and 19-37 were withdrawn as non-elected subject matter.

New claims 38-57 have been added to replace elected and examined claims 1-15 and 18.

Support for new claim 38 can be found in original claims 1 and 2. Support for new claims 39-40 can be found in original claim 1. Further support for new claim 40 can be found in the disclosure, for example, at page 5, lines 4-13. Support for new claim 41 can be found in original claims 3 and 4. Support for new claims 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52 and 53 can be found in original claims 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 18, respectively. Support for new claim 54 can be found in the disclosure, for example, at page 8, lines 18-21. Support for new claim 55 can be found in the disclosure, for example, at page 9, lines 15-20. Support for new claim 56 can be found in the disclosure, for example, at page 5, lines 4-13, at page 6, lines 11-24, and original claims 1-2. Support for new

claim 57 can be found in the disclosure, for example, at page 6, lines 10-24, at page 62, lines 13-30 and original claims 1-2.

Based on the above, it is clear that the new claims correspond to the elected subject matter of previous claims 1-15 and 18. Thus, the new claims should be considered and examined on the merits as the elected invention.

No new matter has been added by the above claim amendments.

Claims 1-37 have been cancelled without prejudice or disclaimer thereto. Applicant reserves the right to file a continuation or divisional application on any cancelled subject matter.

Claims 38-57 are pending upon entry of this amendment.

Applicant thanks the Examiner for the careful examination of this case and respectfully requests reexamination and reconsideration of the case, as amended. Below, Applicant addresses the rejections in the Office Action and explains why the rejections are not applicable to the pending claims as amended.

II. INDEFINITENESS REJECTIONS

Claims 1-15 and 18 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the reasons in items 7-10 on pages 3-4 of the Office Action.

This rejection is respectfully traversed as applied to the amended claims. The rejected claims have been replaced with new claims that better define the claimed subject matter more clearly and distinctively in a non-narrowing manner.

First, it is believed that the present amendment overcomes the rejection in item 7 on page 3 of the Office Action. New claim 38 clearly defines the presence of the nonionic surfactant in the dissolving aqueous medium. Nonetheless, please note that the mode or manner of addition of the nonionic surfactant and the condition or state of the presence of the nonionic surfactant in the dissolving aqueous medium are not limited according to the present invention, and that what is essential is the presence of the nonionic surfactant at least during the process of dissolving the thrombomodulin. As a result, the nonionic surfactant is allowed to be present in the solution containing the thrombomodulin.

Also, new claim 41 makes clear that the nonionic surfactant can be present in the dissolving aqueous solution used for dissolving the soluble thrombomodulin-containing freeze-dried preparation or in the lyophilized thrombomodulin-containing freeze-dried preparation. Such is further discussed throughout the specification. See, for example, at page 12, last paragraph, to page 13, first paragraph. Based on this disclosure, Applicant submits that the skilled artisan would clearly understand the metes and bounds of the claim language.

Second, the present amendment also overcomes the rejection in item 8 on page 3 of the Action. As clear from the language in the new claims, the method results in "a solution containing soluble thrombomodulin, after the dissolving, at a concentration of 10 mg/ml or higher." The skilled artisan would clearly understand this to mean that the concentration of 10 mg/ml or higher applies to the soluble thrombomodulin in the resulting solution after dissolving. Support can be found throughout the disclosure, see for example, page 13, lines 15-22.

Third, the amendment obviates the rejection in item 9 on page 4 of the Action. As evident from the disclosure and the claims, the term "high-concentrated soluble thrombomodulin-containing solution" refers to the fact that the claimed process produces a solution containing a large amount of dissolved soluble thrombomodulin therein. Clear antecedent basis and support for such can be found throughout the new claims and in the disclosure. See for instance, the disclosure, at pages 5 and 6 and at page 13, lines 15-22, wherein the specification discusses the need for preparing a "high-concentrated soluble thrombomodulin having a concentration of 10 mg/ml or higher." See, also the description of such throughout the disclosure, for example, at page 13, lines 15-22. It is also noted that additional dependent claims further specify the amount of dissolved soluble thrombomodulin as "10 mg/ml or higher" (claim 38), etc. This is standard and well accepted terminology in the

industry. The language corresponds to and clearly defines the term "high-concentrated soluble thrombomodulin-containing solution."

It is respectfully submitted that the skilled artisan, upon reading this disclosure and in view of the knowledge in the art, would clearly understand the metes and bounds of the language "high-concentrated soluble thrombomodulin-containing solution" to mean a dissolved soluble thrombomodulin as "10 mg/ml or higher."

Fourth, as to the rejection in item 10, claim 14 has been replaced with new claim 51. Claim 51 uses the language "the nonionic surfactant is present at an amount of 0.01 mg or more per 10 mg of the soluble thrombomodulin" as suggested by the Office.

Based on the amendments and the description, it is believed that the new claims are thus clear, definite and have full antecedent basis.

Thus, the above-noted indefiniteness rejections are believed to be overcome and should be withdrawn.

III. PRIOR ART REJECTIONS

Claims 1-4, 7-9 and 12-15 were rejected under 35 U.S.C. § 102(b) as anticipated by KUNIHIRO (U.S. 5,834,038) for the reasons in items 12-16 on pages 4-7 of the Office Action.

Claims 1-4, 7-10 and 12-15 were rejected under 35 U.S.C. § 103(a) as being obvious over KUNIHIRO in view of JP 11-17190 for the reasons in items 19-24 on pages 7-11 of the Office Action.

Claims 1-4, 7-9, 11-15 and 18 were rejected under 35 U.S.C. § 103(a) as being obvious over KUNIHIRO in view of ZUSHI (U.S. 5,574,007) for the reasons in items 25-30 on pages 12-16 of the Office Action.

Claims 1-9 and 12-15 were rejected under 35 U.S.C. § 103(a) as being obvious over KUNIHIRO in view of KLOKKERS-BETHKE (U.S. 5,335,769) for the reasons in items 31-37 on pages 16-20 of the Office Action.

These rejections are respectfully traversed and will be discussed together below. Note that KUNIHIRO is the primary reference used in each rejection.

First, Applicant will give a general description of the nature of the problem to be solved and discuss the characteristic features of the claimed method. Applicant will then discuss how the cited references, either taken alone or when combined, fail to disclose or suggest these claimed aspects of the invention.

Applicant respectfully submits that the prior art rejections are improper as the Office appears to have misunderstood and disregarded a characteristic feature of the claimed method. Namely, previous claim 1 and now new independent claim 38 clearly recite "to obtain a solution containing soluble

thrombomodulin, after the dissolving, at a concentration of 10 mg/mL or higher." However, the cited prior art references fail to disclose or suggest this particular concentration of 10 mg/mL. In this regard, it is noted that the new claims more clearly specify this characteristic and essential feature of the invention.

The claimed method was achieved on the basis of Applicant's recognition (not known prior to Applicant's priority date) that a lyophilized preparation of soluble thrombomodulin, which contains the soluble thrombomodulin for preparation of an aqueous solution thereof at a concentration of 10 mg/mL or higher, foams just at the time of or just after the addition of a dissolving aqueous solution, such as water for injection. The resulting foam remains in the dissolved solution for a long period of time resulting in a clouded solution. The foaming (that results in the cloudiness of a resulting solution) was found to be formed when the solution had a soluble thrombomodulin concentration of 10 mg/mL or higher.

The claimed method was achieved to solve the above problem of the cloudiness due to the foaming, at the time of the addition of a dissolving aqueous solution to the lyophilized preparation, to prepare a high concentration solution of soluble thrombomodulin.

Attached herewith are photographs (A), (C), and (D), which demonstrate the result of 30 mg/mL, 5 mg/mL, and 10 mg/mL solution of soluble thrombomodulin, respectively, prepared by the addition of a dissolving aqueous solution (in the absence of a nonionic surfactant) to a lyophilized soluble thrombomodulin preparation. Attached photograph (B) indicates physiological saline solution as a clear solution (as a reference not containing thrombomodulin and not forming cloudiness). Note the cloudiness of solution indicated as part (b) is the problem solved by the claimed method, and the bubbles in the part (a) are not relevant to the problem solved by the present invention.

Accordingly, as shown in the attached photographs, one characteristic feature of the claimed method is the high concentration of the soluble thrombomodulin, *i.e.*, 10 mg/ml or higher in the resulting solution.

Another characteristic feature is the means to avoid the cloudiness by the foaming just at the time of the addition of a dissolving aqueous solution. Please note prevention of the formation of bubbles on or near the surface of the resulting solution, which bubbles are indicated in the part (a) of the photographs (A), (C), and (D) and are formed, for example, by shaking the mixture of the lyophilized preparation and the dissolving aqueous solution, is not a direct object of the claimed method.

Instead, the problem solved by the claimed method is the formation of bubbles, especially micro-bubbles (minute bubbles) that retain in the resulting solution to give the cloudiness of the entire solution. See, the discussion of "minute bubble prevention" throughout the disclosure, for example, at page 5, lines 4-14 of the disclosure.

In order to solve the above problem of the formation of the cloudiness as a result of the micro-bubble foaming, which problem was caused (1) just when a dissolving aqueous solution was added to the lyophilized preparation, and (2) the formation of the foams was caused at a concentration of 10 mg/mL or higher, the claimed method was achieved by using a nonionic surfactant at the time of re-dissolving the lyophilized preparation of the soluble thrombomodulin.

It is again noted that the new claims better reflect these characteristic features of the claimed method.

Applicant will now discuss the 102(b) anticipation rejection over KUNIHIRO (which is the primary reference used in each rejection). It is well established that to anticipate a claim, a cited prior art reference must disclose or suggest each and every element of the claimed invention. *See*, M.P.E.P., Eighth Ed., Rev. 6 (September 2007) at § 2131.

Applicant respectfully submits the rejection is improper, because KUNIHIRO fails to disclose or suggest each and

every element of the claimed method, namely, the high concentration of 10 mg/mL of soluble thrombomodulin.

In this regard, KUNIHIRO discloses a composition comprising a soluble thrombomodulin together with one or more ingredients selected from maltose or the like. The reference also discloses a method for preparing said composition, a stabilizer and a method for stabilizing a soluble thrombomodulin, and an agent for prevention of adsorption and a method for prevention.

The Office considers the claims as being anticipated by KUNIHIRO, because the reference discloses a composition containing a soluble thrombomodulin and a nonionic surfactant. The Office concludes one of ordinary skill in the art would be able to prepare a thrombomodulin containing solution of the specified concentration recited in the claim.

Applicant respectfully disagrees. KUNIHIRO fails to provide any description or examples of a concentration of 10 mg/ml or higher. Accordingly, KUNIHIRO cannot be said to disclose or suggest a high concentration of 10 mg/mL or higher of soluble thrombomodulin. As such, the reference cannot disclose each and every element of the claimed method. Thus, KUNIHIRO cannot anticipate the method of independent claim 38. For this reason, claim 38 is novel over KUNIHIRO.

The remaining claims all depend on claim 38. Thus, they too are novel over KUNIHIRO for the same reasons.

Thus, the 102(b) anticipation rejection over KUNIHIRO is untenable and should be withdrawn.

Applicant will now discuss the 103(a) obviousness rejections over the combination of KUNIHIRO, ZUSHI, and KLOKKERS-BETHKE. It is again noted that KUNIHIRO is the primary reference used in each obviousness rejection.

Again, KUNIHIRO fails to disclose or suggest a high concentration of 10 mg/mL or higher of soluble thrombomodulin. KUNIHIRO never even suggests selecting a high concentration, let alone one of 10 mg/mL or higher, for any particular purpose. Therefore, one of ordinary skill in the art would not have been motivated to choose 10 mg/ml or higher concentration to solve the particular problem of foaming encountered by the Applicants.

Note the concentration of 10 mg/mL is a rather high concentration in the art, whereas, in KUNIHIRO, a solution at 1.25 mg/ml of soluble thrombomodulin was prepared and further diluted to 0.003 mg/ml (a relatively low concentration) to study adsorption to a surface of a vessel (see, column 19, experiment 4). Consequently, KUNIHIRO never contemplates a solution higher than 1.25 mg/ml. In this sense, KUNIHIRO actually "teaches away" from choosing the claimed high concentration of 10 mg/ml or higher to achieve the presently claimed method.

In this regard, it is well established that prior art references cannot be combined where a reference teaches away from their combination, such as when a reference would lead the

skilled artisan in a path different from the claimed invention. *See,* M.P.E.P. (Eighth Ed., Rev. 6 (September 2007) at § 2145, X, D, 2. For this reason, it is respectfully submitted that one of ordinary skill in the art would not have combined KUNIHIRO with the secondary references of ZUSHI, and KLOKKERS-BETHKE to arrive at the claimed method.

Further, the problem of the formation of cloudiness by foaming in a solution at the high concentration, prepared by adding a dissolving aqueous solution to a lyophilized preparation, was unknown prior to the priority date of the present application. In fact, Applicant first encountered the above novel problem and achieved the claimed method by using a nonionic surfactant. Accordingly, one of ordinary skill in the art would not have been motivated to make the present claimed method based on the teachings of the cited references as KUNIHIRO did not recognize the problem to be solved.

Further, the objectives in KUNIHIRO were to stabilize a composition containing a soluble thrombomodulin and to prevent adsorption of the thrombomodulin to a surface of a vessel. See, column 4, line 66 to 67, and column 5, lines 1 to 21. Such objectives are clearly different from, and in fact, are unrelated to the claimed method.

For these reasons, it is clear that the primary reference of KUNIHIRO: (1) fails to disclose or suggest the high concentration of 10 mg/mL or higher of soluble thrombomodulin;

(2) actually teaches away from this high concentration; and (3) fails to recognize the very problem solved by the claimed method. Thus, it is respectfully submitted that KUNIHIRO cannot be combined with the secondary references of JP 11-171790, ZUSHI, and KLOKKERS-BETHKE to successfully arrive at the claimed method.

Furthermore, Applicant respectfully submits that the secondary references of JP 11-171790, ZUSHI (U.S. 5,574,007), and KLOKKERS-BETHKE (U.S. 5,335,796) fail to remedy the above-noted deficiencies of KUNIHIRO.

JP 11-171790 discloses an agent comprising a monosaccharide or a disaccharide for preventing degeneration of thrombomodulin.

ZUSHI discloses a substantially pure polypeptide having a characteristic amino acid sequence, including a polypeptide of SEQ ID NO: 1 and the use of urea for cross-linking of a synthetic peptide.

KLOKKERS-BETHKE discloses a process of lyophilization to reduce loss of a lyophilized product by using a glass vessel whose inner surface is coated with a silicone.

However, JP 11-171790, ZUSHI and KLOKKERS-BETHKE all fail to disclose the claimed high concentration of 10 mg/mL or higher of soluble thrombomodulin

Thus, it is clear that none of the cited references disclose the particular high concentration of a soluble thrombomodulin as claimed. As such, it is clear that the

combination of KUNIHIRO with JP 11-171790, ZUSHI and KLOKKERS-BETHKE would not have resulted in the claimed method.

Further, the objective in JP 11-171790 is to provide a stable thrombomodulin composition. This objective is totally different from that of the claimed method of inhibiting or preventing bubbles from being contained in a solution as a result of preparation by dissolving a lyophilized preparation by adding a dissolving aqueous solution. Similarly, the objectives in ZUSHI and KLOKKERS-BETHKE are completely different from that of the claimed method.

Accordingly, one of ordinary skill would not have been motivated to combine the teachings of the cited references to achieve the claimed method.

Based on the above, it is respectfully submitted that the combination of KUNIHIRO with JP 11-171790, ZUSHI, and/or KLOKKERS-BETHKE fails to provide for each and every element of the claimed method. Further, the combined references would not yield predictable results, let alone arrive at the claimed method. This is especially true given: (1) the diverse and different objectives of the cited references; (2) the lack of recognition in the references for the problem solved by the claimed method; and (3) the teaching away in the cited references.

In light of the arguments put forward above, Applicant respectfully submits that neither KUNIHIRO, JP 11-171790, ZUSHI, or KLOKKERS-BETHKE taken alone or in combination, teach, suggest or make obvious each and every element of the claim method. For this reason, independent claim 38 is novel and unobvious over the cited prior art references, either alone or when combined.

The remaining claims depend, either directly or indirectly, on independent claim 38. Accordingly, these claims are also novel and unobvious over the combined prior art references in view of their dependency on claim 38.

Therefore, Applicant respectfully submits that the above-noted 102(b) anticipation rejection and the above-noted 103(a) obviousness rejections are untenable and should be withdrawn.

V. CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

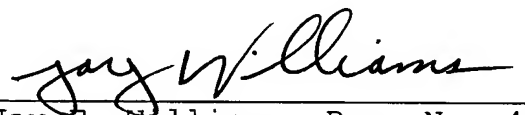
If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any

overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

YOUNG & THOMPSON



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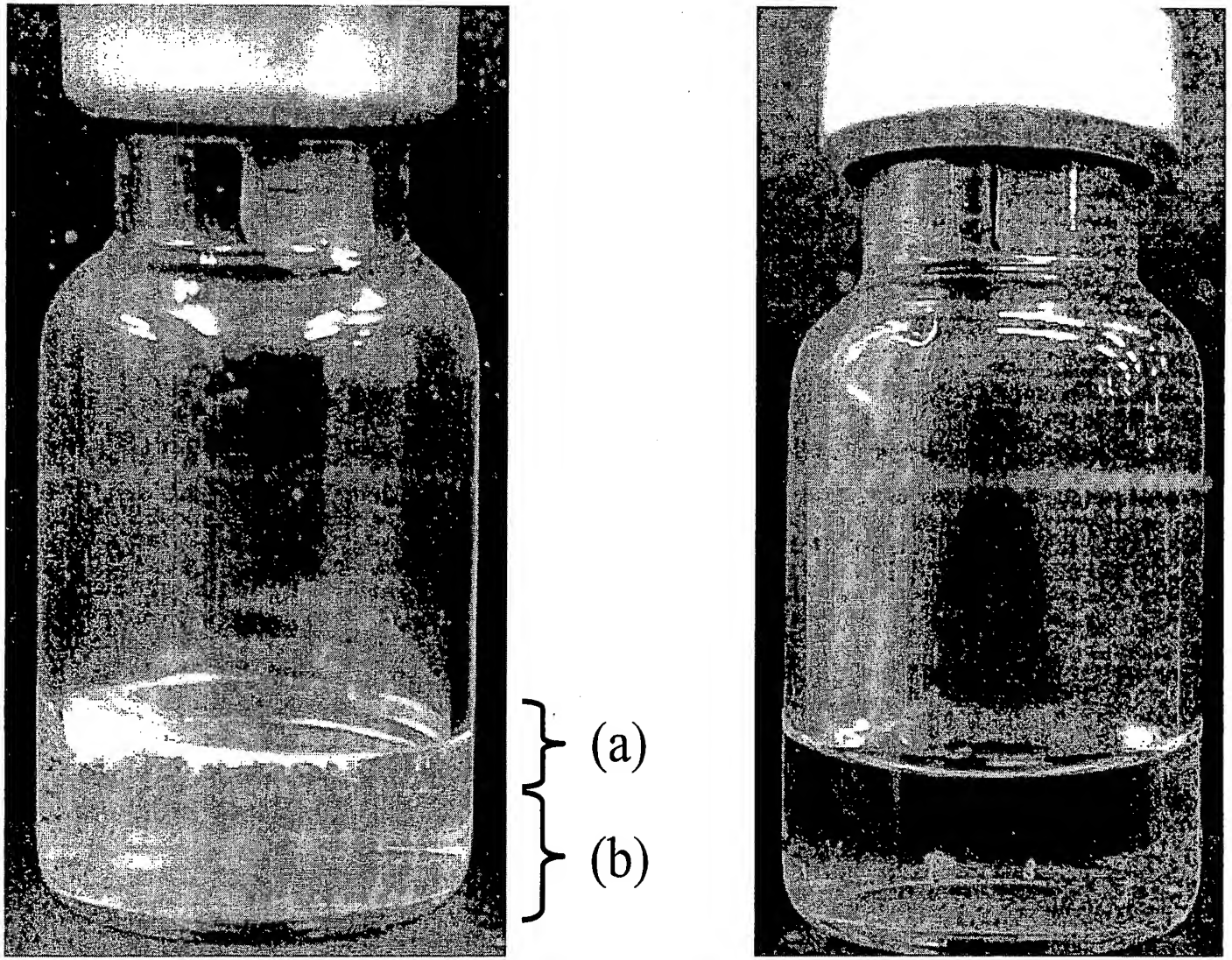
APPENDIX:

The Appendix includes the following item(s):

- photographs (A), (B), (C), and (D).

(A)

(B)



(C)

(D)